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16. ABSTRACT

Historically, mouse skin tumorigenesis has been used to evaluate the tumorigenic effects of complex mixtures including human respiratory carcinogens. This study examines the quantitative relationships between tumor induction in SENCAR mouse skin and the induction of respiratory cancer in man using four well-established human respiratory carcinogens: emissions from coke ovens, roofing tar pots, diesel engines, and cigarettes. The tumor multiplicity data from mouse skin studies using extracts of particulates from each of the four emission sources is compared and their relative potency to the coke oven sample is: coke oven:roofing tar:diesel:cigarette smoke condensate; 1.0:0.20:0.15:0.0011. Using the unit risk (the lifetime probability of respiratory cancer death due to a constant lifetime exposure of 1 $\mu g/m^3$ emissions in the inhaled air) to compare the potency of the four emissions to human respiratory cancer, the relative potency is: coke oven:roofing tar:diesel:cigarette smoke: 1.0:0.39:0.075:0.0024. When fitted to a linear regression the mouse skin tumor data and human lung cancer risks were highly associated, with a correlation constant of 0.95 and a slope value of 0.89. The close association between the two relative potencies suggest that this comparative potency approach can be used in prospective analyses of human respiratory cancer risk to complex emissions, and several examples are proposed. In addition, the similarity of the chemical and toxicological characteristics of complex mixtures is discussed with regard to the prospective use of the comparative potency approach.

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MOUSE SKIN TUMORS AND HUMAN LUNG CANCER: RELATIONSHIPS WITH COMPLEX ENVIRONMENTAL EMISSIONS

Stephen Nesnow[a]

Carcinogenesis and Metabolism Branch

Health Effects Research Laboratory

U.S. Environmental Protection Agency

Research Triangle Park, NC 27711 U.S.A.

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SUMMARY

Historically, mouse skin tumorigenesis has been used to evaluate the tumorigenic effects of complex mixtures including human respiratory carcinogens. This study examines the quantitative relationships between tumor induction in SENCAR mouse skin and the induction of respiratory cancer in man using four well-established human respiratory carcinogens: emissions from coke ovens, roofing tar pots, diesel engines, and cigarettes. The tumor multiplicity data from mouse skin studies using extracts of particulates from each of the four emission sources is compared and their relative potency to the coke oven sample is: coke oven:roofing tar:diesel:cigarette smoke condensate; 1.0:0.20:0.15:0.0011. Using the unit risk (the lifetime probability of respiratory cancer death due to a constant lifetime exposure of 1 $\mu g/m^3$ emissions in the inhaled air) to compare the potency of the four emissions to human respiratory cancer, the relative potency is: coke oven:roofing tar:diesel:cigarette smoke: 1.0:0.39:0.075:0.0024. When fitted to a linear regression the mouse skin tumor data and human lung cancer risks were highly associated, with a correlation constant of 0.95 and a slope value of 0.89. The close association between the two relative potencies suggest that this comparative potency approach can be used in prospective analyses of human respiratory cancer risk to complex emissions, and several examples are proposed. In addition, the similarity of the chemical and toxicological characteristics of complex mixtures is discussed with regard to the prospective use of the comparative potency approach.

INTRODUCTION

Skin has been used as a target system for studying chemical carcinogens and complex mixtures since the finding of Percival Pott that young male chimney sweeps had an unusually high incidence of scrotal tumors (Pott, 1775). The etiological factor identified in this rare tumor type was chimney soot, which, in combination with lack of personal hygiene, resulted in this preventable cancer. In 1915, rabbit ear skin was used by Yamagawa and Ichikawa (1915) to study the role of hyperplasia in the cancer process using coal tar to induce tumors. Complete carcinogenesis in mouse skin was used as early as 1922 to identify carcinogens in organic extracts of particulate samples and to try to link these materials to the etiology of human cancer when Passey (1922) found that that ethereal extracts of coal chimney soot produced both warts (papillomas) and cancers (carcinomas) when applied repetitively to the depilated backs of mice. Campbell (1934, 1939) confirmed these results with coal soot and also reported the carcinogenic activity of road dust extracts on mouse skin. Kotin and coworkers examined the carcinogenic effects of organic extracts of air particulate samples from the Los Angeles area (Kotin et al., 1954a). These extracts produced both malignant and benign tumors when applied repeatedly to the backs of C57BL/6 mice. Wynder and Hoffmann reported studies on the administration of air particulate extracts from the Detroit area to Swiss ICR mice (Wynder and Hoffmann, 1965). Kotin et al. (1954b) and Wynder and Hoffmann (1962) also studied the carcinogenic effects of organic extracts of particulate emissions from gasoline engines; both concluded that these extracts produce tumors in mice and Kotin et al. (1955) found that extracts from diesel engine particulates were tumorigenic. Von Haam and Mallette (1952) and Vosamae

(1979) were able to induce tumors in mice by applying extracts of industrial carbon black and oil shale soot, respectively.

The purpose of this study is to examine the quantitative relationships between the formation of mouse skin tumors by known human complex mixture respiratory carcinogens and human respiratory cancer risk and to explore methods which will apply these relationships to similar etiological agents associated with human neoplasia.

RESULTS AND DISCUSSION

Selection of Complex Environmental Emissions:

Four complex environmental mixtures were bioassayed on SENCAR mouse skin: coke oven emissions, diesel exhaust, roofing tar emissions, and cigarette smoke condensate. These emissions have previously been shown to be associated with the induction of respiratory cancer in exposed populations. Coke oven workers have been reported to display an increased rate of lung cancer (Mazumdar et al., 1975). For mouse skin studies, a representative sample of coke oven emissions was obtained from particulates collected from the top of a coke oven battery. Emissions from roofing tar pots have been causally associated with respiratory cancer in exposed populations as shown by Hammond et al. (1976). A sample of roofing tar emissions was collected for mouse skin studies from a conventional tar pot. Several major epidemiological studies have related cigarette smoking and respiratory cancer in humans, the most notable a study by Doll and Peto (1978). For mouse skin studies a acetone-water condensate of cigarette smoke was collected by the method of Patel (1977) using a reference cigarette in a cigarette smoking machine. Garshick et al. (1987, 1988) have reported a causal association between exposure to diesel exhaust and lung cancer in railroad workers. For mouse skin studies,

diesel particulate samples were collected from a 1978 Oldsmobile 350 vehicle using No. 2 diesel fuel. Dichloromethane extracts of these four emissions were prepared as previously described (see Nesnow et al., 1982, 1983 for details of sample collection and preparation).

Mouse Skin Studies:

The tumorigenic effects of these complex environmental mixtures were determined using male and female SENCAR mice exposed to five-doses of each mixture (40/sex) and each of these materials were evaluated using both the tumor initiation and complete carcinogenesis protocols (data not discussed). In the tumor initiation protocol, the organic extract was administered to the shaved backs of SENCAR mice during the first week of treatment. Tumor promotion followed with twice-weekly applications of TPA (4.0 μg/week) for 26 wk (Nesnow et al., 1982, 1983).

Two statistical procedures were developed to analyze mouse skin tumor data. The first analysis, based on tumor incidence data, used a log-probit model and included the observations of tumors occurring in the TPA controls. The TD_{50} and TD_{25} was then directly estimated as a function of these fitted parameters, and 95% confidence intervals were constructed. The second statistical model employed tumor multiplicity data, featured a nonlinear Poisson model with a background correction term, and calculated the number of excess papillomas per mouse over background at a dose of 1 mg organic extract (Nesnow et al., 1983).

To compare the potency estimates between samples, the results from the two sexes for each sample were combined as no sex differences were observed (Nesnow et al., 1983). Based on mouse skin papilloma multiplicity data, the relative potency (coke oven = 1.0) was: coke oven:roofing tar:diesel:cigarette

smoke condensate; 1.0:0.20:0.15:0.0011 [Table 1]. When comparing the tumor incidence data, the relative ranking was coke oven:roofing tar:diesel:cigarette smoke condensate; 1.0:0.22:0.16:0.0017 (Albert et al., 1983).

Calculation of the Unit Risks:

The basis for comparing human cancer risks was the unit risk, defined as the lifetime probability of respiratory cancer death due to a constant lifetime exposure of 1 $\mu g/m^3$ benzene-soluble organic (BSO)-equivalent emissions in the inhaled air (Albert et al., 1983) The unit risk estimates for coke oven emissions, roofing tar emissions, and cigarette smoke were based on a linear nonthreshold extrapolation model and have been reported in detail elsewhere [Table 2] (Albert et al., 1983). Although there are several reports which clearly associate exposure to diesel exhaust and lung cancer in man (Garshick et al., 1987, 1988), at present there is no exposure data available to calculate the unit risk for diesel. It is to be noted that this information should be forthcoming as Hammond et al. (1989) and Woskie et al. (1988a,b) have reported preliminary exposure estimates. However, the unit risk for diesel exposure can be calculated from diesel exhaust rodent inhalation studies. Several chronic lifetime inhalation studies on diesel emissions have been reported, strongly indicating that diesel exhaust is a rodent lung carcinogen (McClellan, 1987). One of these diesel inhalation studies used F344 rats which were exposed to the exhaust of a 1980 Oldsmobile, a vehicle similar to that used in the previously reported SENCAR mouse skin studies (Mauderly et al., 1987). Applying the data from this study to a linearized multistage extrapolation model, Albert and Chen (1986) estimated the risk to be 1.2×10^{-5} lifetime risk/μg particulates/m^3. Adjusting this

value for the % organic materials extracted from the particulates (using the value from Albert et al., 1983) the unit risk becomes 0.7×10^{-4} lifetime risk/mg organics/m^3. Therefore, the relative potency of these human respiratory carcinogens is coke oven:roofing tar:diesel:cigarette smoke: 1.0:0.39:0.075:0.0024 (Table 2).

Relationships Between the Rodent and Human Data:

The method chosen to compare the potency of these complex environmental mixtures based on the mouse skin, rodent inhalation, and cancer epidemiology was the constant relative potency assumption as applied to human respiratory cancer (Albert et al., 1983; Lewtas et al., 1983) [Fig. 1]. Under this assumption, the relationship between the potency of inducing respiratory cancer in man of two human carcinogens, X and Y, is proportional to the relationship between the potency of X and Y in a surrogate bioassay system, in this case, mouse skin tumorigenesis. The proportionality constant K can be measured experimentally from pairs of human respiratory carcinogens. The more similar the K values for pairs of respiratory carcinogens, the more credence can be put in this extrapolation approach.

To test the comparative potency-relative constant potency hypothesis, a series of K values were calculated based on the mouse skin tumor initiation tumor multiplicity data and the unit lung cancer risk estimates for coke oven emissions, roofing tar emission, and cigarette smoke condensate. Using a 2 x 2 pairing comparison, the K values ranged from 0.25-4.0 or approximately 10-fold, with a mean of 1.7 and a standard deviation of 1.3 (Table 3). The correlation between the mouse skin tumor initiation-tumor multiplicity data and the unit risk estimates was quite good, with a correlation constant of 0.95 and a slope value of 0.89 (Fig. 2). The correlation constant and slope

values for coke oven, roofing tar and cigarette smoke were 0.99 and 0.92 respectfully (Nesnow, 1989), suggesting that the diesel sample does not alter the correlation significantly.

The close agreement between the two rankings, which use completely different scientific bases, assumptions, tumor incidences, and target tissues, confirms the confidence in the comparative potency assumption and serves to strengthen the argument for the use of the comparative potency method in risk assessment.

Future Directions:

In order to test the potential applicability of the comparative potency approach, prospective analyses combined with laboratory investigations are needed on populations exposed to complex environmental mixtures. Such analyses would use mouse skin data to predict the unit risk of lung cancer from exposure to potential human respiratory carcinogens. These predicted unit risks would then be compared to the unit risk derived from epidemiological studies. There are several populations recently reported in the literature which might be used. One population is a group of communes in Xuan Wei County in Yunnan Province, People's Republic of China (Mumford et al., 1987) and another population are Swedish Chimney sweeps (Gustavsson et al., 1987).

The rates of lung cancer in Xuan Wei County are six-times the mortality rates for Yunnan Province for males and 16 times those for females. Within Xuan Wei County there are 20 communes, and lung cancer mortality rates vary by commune. The etiological factor that is associated with lung cancer incidence and that correlates with commune practices is the burning of fuel in unvented houses. The fuel most commonly used in high-mortality lung cancer communes is

a smoky coal mined in the county. This fuel-burning for heat and cooking purposes creates a very high level of indoor pollutants, both particulate and gaseous. Under a current U.S. EPA-People's Republic of China Cooperative Research Program, particulate samples have been collected at Xuan Wei and are being subjected to evaluation on SENCAR mouse skin as tumor initiators and complete carcinogens. Xuan Wei County thereby provides a test for the comparative potency model for complex emissions.

Gustavsson et al. (1987) have recently described a cohort study of over 5000 Swedish chimney sweeps in which mortality from lung cancer as well as other tumors were significantly increased and not explained by smoking habits. It is believed that exposure to soot particles containing PAH is responsible for the excess cancer deaths. If exposure data were developed for this cohort and mouse skin tumor data developed from the soot extracts, the comparative potency model could be applied to this population.

Use of Similarity to Apply the Comparative Potency Approach to New Mixtures:

A key element in the prospective use of the comparative potency approach is the determination of the similarity of the mixture being evaluated to those mixtures already in the matrix. The mixtures in the matrix are from a fairly broad representation of chemical and physical processes involving a variety of fuels. Coke oven emissions result from the reductive conversion of coal into coke; diesel emissions from the combustion of diesel fuel, roofing tar emissions from the distillation of coal tar and cigarette smoke from the combustion of tobacco. However, all these mixtures contain some common elements in composition such as polycyclic aromatic hydrocarbons (Austin et al., 1985), a chemical class associated with strong neoplastic responses in experimental animals (Grimmer et al., 1987).

The determination of similarity can be made by considering both the chemical composition and biological activity of the mixtures, and four major approaches are discussed: chemical class; indicator constituents; short-term tests; and genetic activity profiles. These analyses are presented as separate entities, but it is recognized that some of these overlap in concept and practice, and may be used in concert in the evaluative process towards defining the similarity of mixtures.

Chemical or Chemical Class Similarity:

One approach to the evaluating the similarity of complex mixtures is to incorporate as much of the chemistry of the mixtures as possible into the evaluative process. If similarities in chemical structure or in chemical class exist within multi-component mixtures, then these similarities can be applied toward a convincing argument that toxicological similarities will also exist. Examples of chemical similarities can be found within various samples of mixture classes (e.g. emissions from woodstoves, diesel engines) where a combination of chemical fractionation and short-term bioassay can identify related mixtures (Lewtas et al., 1988).

Indicator Constituents as Measures of Similarity:

A second approach to the determination of similarity of mixtures is to use indicator constituents. Indicator constituents may be used to predict tumorigenic effects from one mixture to another within a mixture class assuming that the indicator contributes a significant extent to the tumorigenic effects. B(a)P may be used as an indicator constituent in some complex mixtures from the same type of emission source as the tumor levels from a series of B(a)P containing diesel emissions from different engines were linearly related to B(a)P levels. However, in the same analysis, B(a)P levels

in complex mixtures from different mixture classes (e.g., coke oven, roofing tar) were not linearly related to tumor levels (Nesnow et al., 1983). A similar finding was reported in which cigarette smokers and roofing tar workers were compared for their exposure to B(a)P and lung cancer incidence. The roofing tar workers received much greater exposure to B(a)P than the cigarette smokers but exhibited a markedly reduced lung cancer incidence when compared to the smokers (NRC, 1988).

Short-term Test Similarity:

A third approach to the determination of similarity of complex mixtures is to use short-term test data obtained on the mixtures. Short-term tests for DNA damage, gene mutation, aneuploidy, chromosomal damage, and cell transformation, performed in prokaryotes and eukaryotes and studied in vitro and in vivo have been used to characterize and evaluate the genetic toxicity of chemicals and mixtures. Data from these tests can provide valuable information in the evaluation process for determining the similarity of mixtures (Austin et al., 1985; Lewtas, 1983; Williams and Lewtas, 1985). Some complex mixture classes have unique characteristics that can be used to identify their similarity (e.g. nitroarenes in diesel exhaust). It is emphasized that results from the testing of mixtures in a single short-term test, however valuable, only measure a portion of the total biological activity of a multi-component mixture (e.g., the measurement of point mutation by Salmonella typhimurium).

Genetic Activity Profile Similarity:

In addition to similarity analysis by single component short-term test methods for genetic and related effects, a holistic view can be applied to mixture analysis by use of the Genetic Activity Profiles [GAP] (IARC, 1987a;

Waters et al., 1988a). These profiles combine both a qualitative and quantitative view of the genetic toxicity of chemicals and mixtures over a complete range of genetic toxicity endpoints and therefore measure a broad range of toxicological damage. Similarities in GAP for different samples of a mixture can be used as a measure of mixture similarity or dissimilarity. The techniques for matching GAP to identify chemicals with similar GAP patterns have been developed and applied to identifying structurally and biologically similar chemicals (Waters et al., 1988b). This is a particularly strong approach to mixture evaluation of carcinogens as many combustion mixtures respond very well in short-term tests for genetic toxicity. A limitation, however, in using the profile technique for evaluation of mixture similarity is the inability of genetic tests to detect the presumptive carcinogenic activity of chemicals which exert their activity by other than genetic mechanisms (non-genotoxic carcinogens) in that these tests (with the exception of cell transformation tests) are generally not included in the profile method. A fact mitigating this problem is that approximately 90% of the human carcinogens identified to date through the IARC process seem to be genetically active (genotoxic) [IARC, 1987a,b]. Whether this is a result of a selective process or really representative of human carcinogens as a group remains to be determined. A potential solution to this problem is to identify those chemicals in mixtures which might exert their carcinogenic activity by non-genotoxic mechanisms. This could be accomplished through chemical analysis, bioassay directed fractionation, and other techniques. These test results could then be incorporated into the GAP for GAP matching analyses. Recently, GAP analyses have been applied to complex mixtures and these results are reported in this volume by Waters et al., (1989).

In conclusion, the comparative potency approach shows great promise as a method of estimating the potential risks from man's exposure to complex environmental mixtures. The relatively good fit of the four complex emissions within the comparative potency framework is encouraging for the future use of this method for predicting the human health effects of complex environmental emissions for risk evaluations and risk assessment. Continued testing and evaluation of this approach is necessary to reinforce its utility and accuracy.

REFERENCES

Albert, R.E., Chen, C. (1986) U.S. EPA diesel studies on inhalation hazards. In: Ishinishi, N., Koizumi, A., McClellan, R.O., and Stober, W., eds. Carcinogenic and Mutagenic Effects of Diesel Engine Exhaust, New York, Elsevier Science Publishers, pp. 411-419.

Albert, R.E., Lewtas, J., Nesnow, S., Thorslund, T.W., & Anderson, E. (1983) Comparative potency method for cancer risk assessment: Application to diesel particulate emissions. Risk Anal. 3, 101-117.

Austin, A.C., Claxton, L.D., and Lewtas, J. (1985) Mutagenicity of the fractionated organic emissions from diesel, cigarette smoke condensate, coke oven, and roofing tar in the Ames assay. Environ. Mutagen., 7, 471-487.

Campbell, J.A. (1934) Cancer of skin and increase in incidence of primary tumours of lung in mice exposed to dust obtained from tarred roads. Brit. J. Exp. Path., 15, 287-294.

Campbell, J.A. (1939) Carcinogenic agents present in the atmosphere and incidence of primary lung tumours in mice. Brit. J. Exp. Pathol., 20, 122-132.

Doll, R, Peto, R. (1978) Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. J. Epidemiol. Community Health, 32, 303-313.

Garshick, E., Schenker, M.B., Munoz, A., Segal, M., Smith, T.J., Woskie, S.R., Hammond, S.K., Speizer, F.E. (1987) A Case-control study of lung cancer and diesel exhaust exposure in railroad workers. Am. Rev. Respir. Dis. 135, 1242-1248.

Garshick, E., Schenker, M.B., Munoz, A., Segal, M., Smith, T.J., Woskie, S.R., Hammond, S.K., Speizer, F.E. (1988) A retrospective cohort study of lung cancer and diesel exhaust exposure in railroad workers. Am. Rev. Respir. Dis. 137, 820-825.

Grimmer, G. Brune, H., Deutsch-Wenzel, R., Dettbarn, G., Jacob, J., Naujack, K.-W., Mohr, U. and Ernst, H. (1987) Contribution of polycyclic aromatic hydrocarbons and nitro-derivatives to the carcinogenic impact of diesel engine exhaust condensate evaluated by implantation into the lungs of rats. Cancer Lett. 37, 173-180.

Gustavsson, P., Gustavsson, A., and Hogstedt, C (1987) Excess mortality among Swedish chimney sweeps. Brit. J. Ind. Med., 44, 738-743.

Hammond, E.D., Selikoff, I.J., Lawther, P.L., Seidman, H. (1976) Inhalation of benzopyrene and cancer in man. Ann. NY Acad. Sci., 271, 116-124.

Hammond, S.K., Smith, T.J., Woskie, S.R., Leaderer, B.P., and Bettinger, N. (1988) Markers of exposure to diesel exhaust and cigarette smoke in railroad workers. Am. Ind. Hyg. Assoc. J. 49, 516-522.

IARC (1987a) IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans, Genetic and Related Effects: An Updating of Selected IARC Monographs from Volumes 1 to 42, Supplement 6, Lyon.

IARC (1987b) IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans, Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs from Volumes 1 to 42, Supplement 7, Lyon.

Kotin, P., Falk, H.L., Mader, M.P., Thomas, M. (1954a) Aromatic hydrocarbons, I: presence in the Los Angeles atmosphere and the carcinogenicity of atmospheric extracts. AMA Arch. Ind. Hyg. Occup. Med., 9, 153-163.

Kotin, P., Falk, H.L., Thomas, M. (1954b) Aromatic hydrocarbons, II: presence in the particulate phase of gasoline-engine exhausts and the carcinogenicity of exhaust extracts. AMA Arch. Ind. Hyg. Occup. Med., 9, 164-177.

Kotin, P., Falk, H.L., Thomas, M. (1955) Aromatic hydrocarbons, III: presence in the particulate phase of diesel-engine exhausts and the carcinogenicity of exhaust extracts. AMA Arch. Ind. Health, 11, 113-120.

Lewtas, J. (1983) Evaluation of the mutagenicity an carcinogenicity of motor vehicle emissions in short-term bioassays. Environ. Health Perspect., 47, 141-152.

Lewtas, J. (1988) Genotoxicity of complex mixtures: Strategies for the identification and comparative assessment of airborne mutagens and carcinogens from combustion sources. Fund. Appl. Toxicol., 10, 571-589.

Lewtas, J., Nesnow, S., Albert, R.E. (1983) A comparative potency method for cancer risk assessment: Clarification of the rationale, theoretical basis, and application to diesel particulate emissions. Risk Anal., 3, 133-137.

McClellan, R.O. (1987) Health effects of exposure to diesel exhaust particles. Ann. Rev. Pharmacol. Toxicol. 27, 279-300.

Mauderly, J.L., Jones, R.K., Griffith, W.C., Henderson, R.F., McClellan, R.O. (1987) Diesel exhaust is a pulmonary carcinogen in rats exposed chronically by inhalation. Fund. Appl. Toxicol., 9, 208-221.

Mazumdar, S., Redmond, C.K., Sollecito, W., Sussman, N. (1975) An epidemiological study of exposure to coal tar pitch volatiles among coke oven workers. J. Air Pollut. Control Assoc., 25, 382-389.

Mumford, J.L., He, X.Z., Chapman, R.S., Cao, S.R., Harris, D.B., Li, X.M., Xian, Y.L., Jiang, W.Z., Xu, C.W., Chuang, J.C., Wilson, W.E., Cooke, M. (1987) Lung cancer and indoor air pollution in Xuan Wei, China. Science, 235, 217-220.

National Research Council, National Academy of Science Health (1988) Complex Mixtures, Methods for In Vivo Toxicity Testing, Washington, DC, National Academy of Science Press, 227 pp.

Nesnow, S. (1989) Mouse skin tumors as predictors of human lung cancer for complex emission: an overview. In: Slaga, T.J., Klein-Szanto, A.J.P., Boutwell, R.K., et al., Skin Carcinogenesis: Mechanisms and Human Relevance, Alan R. Liss, Inc., pp. 347-361.

Nesnow, S., Triplett, L.L., Slaga, T.J. (1982) Comparative tumor-initiating activity of complex mixtures from environmental particulate emissions on SENCAR mouse skin. J. Natl. Cancer Inst., 68, 829-834.

Nesnow, S., Triplett, L.L., and Slaga, T.J. (1983) Mouse skin tumor initiation-promotion and complete carcinogenesis bioassays mechanisms and biological activities of emission samples. Environ. Health Perspect., 47, 255-268.

Passey, R.D. (1922) Experimental soot cancer. Brit. Med. J. 2, 1112-1113.

Patel, A.R. (1977) Preparation and monitoring of cigarette smoke condensate samples. In: Gori, G.B., ed., Report No. 3, Toward Less Hazardous Cigarettes - The Third Set of Experimental Cigarettes. DHEW Publication No. (NIH) 77-1280, pp. 67-80.

Pott, P. (1775) Chirurgical observations relative to the cataract, the polypus of the nose, the cancer of the scrotum, the different kinds of ruptures, and the mortifications of the toes and feet. In: Hawes, L., Clarke, W. and Collins, R, eds., The Chirurgical Works of Percival Pott, Vol. 5, London.

Von Haam, E., Mallette, F.S. (1952) Studies on the toxicity and skin effects of compounds used in the rubber and plastics industries, III: carcinogenicity of carbon black extracts. AMA Arch. Ind. Hyg. Occup. Med., 6, 237-242.

Vosamae, A.I. (1979) Carcinogenicity studies of Estonian oil shale soots. Environ. Health Perspect., 30, 173-176.

Waters, M.D., Stack, H.F., Brady, A.L., Lohman, P.H.M., Haroun, L., and Vainio, H. (1988a) Use of computerized data listings and activity profiles of genetic and related effects in the review of 195 compounds. Mutation Res, 205, 295-312.

Waters, M.D., Stack, H.F., Rabinowitz, J.R., and Garrett, N.E. (1988b) Genetic activity profiles and pattern recognition in test battery selection. Mutation Res, 205, 119-138.

Waters, M.D., Stack, H.F., Claxton, L.D., and Graedel, T.E. (1989) Genetic activity profiles--application in assessing potential carcinogenicity of complex environmental mixtures. In: IARC Publication, in press.

Williams, K., and Lewtas, J. (1985) Metabolic activation of organic extracts from diesel, coke oven, roofing tar, and cigarette smoke emissions in the Ames assay. Environ. Mutagen., 7, 489-500.

Woskie, S.R., T.J. Smith, S. K. Hammond, M.B. Schenker, E. Garshick, and F.E. Speizer (1988a) Estimation of the diesel exhaust exposures of railroad workers: I. Current exposures. Am. J. Ind. Med., 13, 381-394.

Woskie, S.R., T.J. Smith, S. K. Hammond, M.B. Schenker, E. Garshick, and F.E. Speizer (1988b) Estimation of the diesel exhaust exposures of railroad workers: I. National and historical exposures. Am. J. Ind. Med., 13, 395-404.

Wynder, E.L., Hoffmann, D. (1962) A study of air pollution carcinogenesis, III: carcinogenic activity of gasoline engine exhaust condensate. Cancer, 15, 103-108.

Wynder, E.L., Hoffmann, D. (1965) Some laboratory and epidemiological aspects of air pollution carcinogenesis. J. Air Pollut. Control Assoc., 15, 155-159.

Yamagawa, K., Ichikawa, K. (1915) Experimentelle studies uber die pathogenese der epithelialgeschwulste. Mitteilungen Med. Facultat Kaiserl. Univ. Tokyo 15, 295-344.

Table 1. Induction of Papillomas in SENCAR Mouse Skin by Human Respiratory Carcinogens under a Tumor Initiation Protocol

Carcinogen	Papillomas/mouse at 1 mg organics (95% Confidence Intervals)	Relative Rank[a]	TD_{25}, Dose in mg yielding 25% mice with papillomas	Relative Rank[a]
Coke oven	2.1[b] (1.9-2.4)	1.0	0.16[c]	1.0
Roofing tar	0.40[b] (0.3-0.6)	0.20	0.71[c]	0.22
Diesel	0.31[d]	0.15	1.0[d]	0.16
Cigarette Smoke	0.0024[d]	0.0011	92[d]	0.0017

[a]Values are normalized to the coke oven sample.

[b]Values based on statistical analyses of the papilloma incidence data by a log-Probit model with background correction (Albert et al., 1983).

[c]Values based on statistical analyses of the papilloma multiplicity data by a Poisson model with background correction (Albert et al., 1983).

[d]Values based directly on multiplicity or incidence data (Nesnow et al., 1982; Nesnow, Triplett, and Slaga, unpublished observations).

Table 2. Human Lung Cancer Unit Risks[a] for Four Complex Mixtures

Emission Source	Human Lung Cancer Unit Risk	Relative Rank
Coke oven[b]	9.3×10^{-4}	1.0
Roofing tar[b]	3.6×10^{-4}	0.39
Diesel[c]	0.7×10^{-4}	0.075
Cigarette smoke[d]	2.2×10^{-6}	0.0024

[a]Lifetime risk/mg organics/m^3. All values except the diesel were based on epidemiological observations (Albert et al., 1983).

[b]Based on the linear non-threshold model.

[c]The diesel value was based on rat inhalation data (Albert and Chen, 1986) and was adjusted for the % organics on the particulates.

[d]Geometric mean of the limits from the linear and quadratic model.

Table 3. Proportionality Constants (K) for Pairs of Human Respiratory Carcinogens[a]

	Roofing Tar	Diesel	Cigarette Smoke
Coke Oven	2.0	0.51	2.1
Roofing Tar	--	0.25	1.0
Diesel	--	--	4.0

[a]Calculated from each unique pair of human respiratory carcinogens according to the equation in Figure 1 and using the mouse skin tumor multiplicity and human cancer unit risk data. By convention, the more active agent was placed in the numerator.

FIGURE LEGENDS

FIGURE 1. The comparative potency (constant relative potency) assumption as applied to human respiratory cancer. X and Y represent human respiratory carcinogens while K is the proportionality constant.

FIGURE 2. Correlation between SENCAR mouse skin tumorigenicity (tumor initiation-tumor multiplicity) and unit cancer risks for four human respiratory carcinogens. The correlation constant is 0.95.

$$\frac{\text{POTENCY [LUNG CANCER IN MAN] OF X}}{\text{POTENCY [LUNG CANCER IN MAN] OF Y}} = K \left[\frac{\text{POTENCY [MOUSE SKIN] OF X}}{\text{POTENCY [MOUSE SKIN] OF Y}} \right]$$

FIG. 1

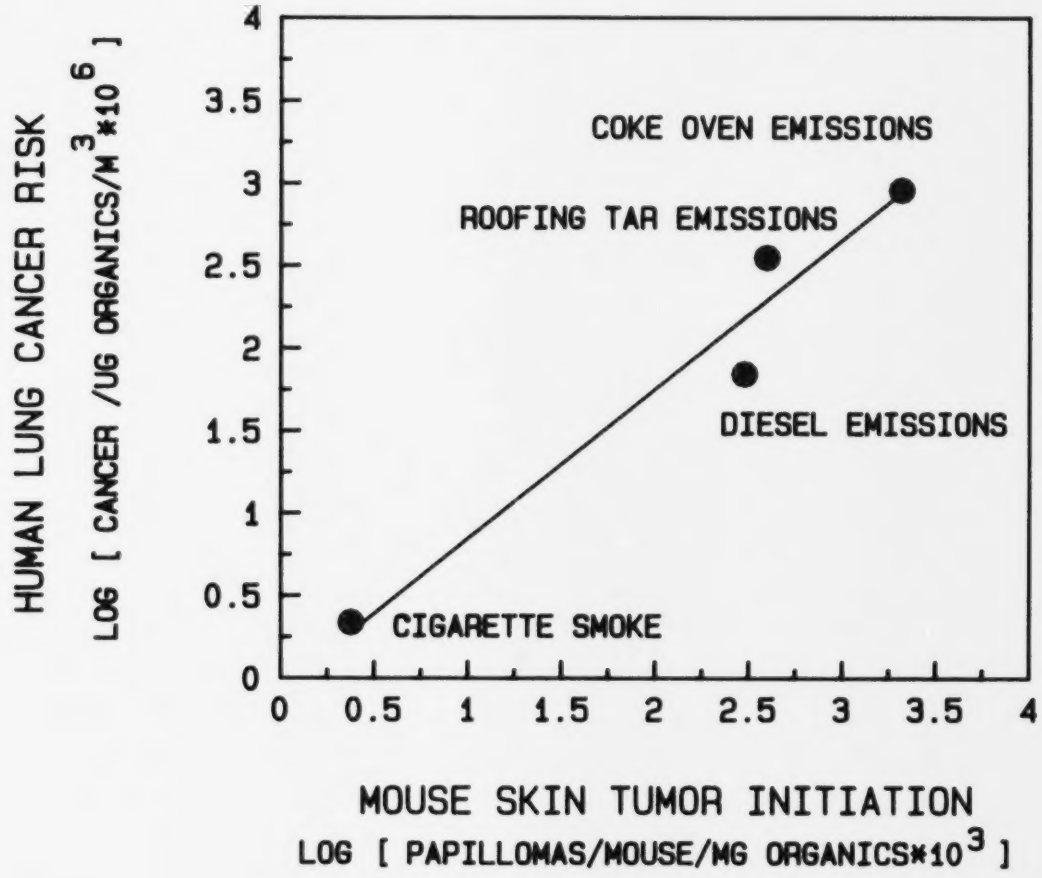
HUMAN LUNG CANCER RISK
LOG [CANCER /UG ORGANICS/M3*10^6]
4
3.5
3
2.5
2
1.5
1
0.5
0
COKE OVEN EMISSIONS
ROOFING TAR EMISSIONS
DIESEL EMISSIONS
CIGARETTE SMOKE
0
0.5
1
1.5
2
2.5
3
3.5
4
MOUSE SKIN TUMOR INITIATION
LOG [PAPILLOMAS/MOUSE/MG ORGANICS*10^3]

FIG. 2